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(54) Title: METHODS FOR TREATMENT AND PREVENTION OF INFECTIONS

(57) Abstract

The present invention provides methods, kit, and pharmaceutical compositions for treating or preventing an infection in a mammal comprising the administration of an amount effective for treating or preventing an infection of angiotensinogen, angiotensin I (AI), AI analogues, AI fragments and analogues thereof, angiotensin II (AII), AII analogues, AII fragments or analogues thereof or AII AT_2 type 2 receptor agonists.

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METHODS FOR TREATMENT AND PREVENTION OF INFECTIONS

Cross-Reference

This application is a continuation-in-part of U.S. Provisional Application Serial Nos. 60/081,262 filed April 9, 1998 and 60/089024 filed June 12, 1998, both references herein incorporated by reference in their entirety.

Background of the Invention

Humans are susceptible to infection by a variety of pathogens, including bacteria, viruses, and other parasites. Such infections pose a significant health risk for the human population in general. One example of bacterial infection is sepsis, which can occur in hospitalized patients having underlying diseases or conditions that render them susceptible to bloodstream invasion or in burn, trauma or surgical patients. (U.S. Patent No. 5,714,469, hereby incorporated by reference in its entirety). In many cases of sepsis, the predominant pathogen is *Escherichia coli,* although other gram-negative bacteria such as the *Klebsiella-Enterobacter-Serratia* group and *Pseudomona,* and gram positive microbes such as Staphylococcus, can be the causative pathogen. The genitourinary tract, gastrointestinal tract and respiratory tract are the most frequent sources of sepsis. Other common foci are wound, burn, and pelvic infections and infected intravenous catheters.

A serious consequence of bacterial sepsis often is septic shock. Gram negative sepsis is a disease syndrome resulting from the systemic invasion of gram negative rods and subsequent endotoxemia. (U.S. Patent No. 5,698,198,

incorporated by reference herein in its entirety) The severity of the disease ranges from a transient, self-limiting episode of bacteremia to a fulminant, life-threatening illness often complicated by organ failure and shock. The disease is often the result of invasion from a localized infection site, or may result from trauma, wounds, ulcerations or gastrointestinal obstructions. The symptoms of gram negative sepsis include fever, chills, pulmonary failure and septic shock (severe hypotension).

Gram negative infections are particularly common among patients receiving anti-cancer chemotherapy and immunosuppressive treatment. (U.S. Patent No. 5,698,198) Infections in such immuno-compromised hosts characteristically exhibit resistance to many antibiotics, or develop resistance over the long course of the infection, making conventional treatment difficult. The ever increasing use of cytotoxic and immunosuppressive therapy and the natural selection for drug resistant bacteria by the extensive use of antibiotics have contributed to gram negative bacteria evolving into pathogens of major clinical significance.

Septic shock is a major cause of death in intensive care units. It is estimated that over 700,000 patients become susceptible to septic shock-causing bacterial infections each year in the United States alone. Of these, 160,000 actually develop septic shock, resulting in 50,000 deaths annually. (U.S. Patent No. 5,698,198) Despite advances in respiratory support technology and antibiotic therapy, the mortality rate for septic shock remains in excess of 40%. (U.S. Patent No. 5,714,469) In fact, mortality for established septic shock has decreased very little over the past 50 years. (*Arch. Intern. Med.* 88:467-488 (1951)) Although effective antibiotics are available, and there is an increased awareness of the septic shock syndrome, the incidence of septic shock over the last several decades has actually

increased. With the appreciation that antimicrobial agents have failed to completely abrogate septic mortality, it is clear that other agents must be developed to rectify the deficiencies of current established therapy for septic shock, as well as for other types of infections, including but not limited to peritonitis, bacteremia, endotoxemia, and viral and parasitic infections.

Treatment of bacterial diseases with antibiotics is further complicated by the ability of the organisms to develop antibiotic resistance. The magnitude of the problem is further amplified by the extreme difficulty of total eradication, and the frequent reappearance of the same strain even after apparently successful elimination. The inability to eliminate the carrier state by any of the currently known methods and the prevalence of the new antibiotic resistant hospital strains have added a new dimension to the frustrating situation. The development of such multiple antibiotic resistant strains of the organism further suggests the desirability of investigating additional means of combating bacterial infections.

Summary of the Invention

The present invention provides methods and kits for treating or preventing infection comprising the administration of an amount effective for treating or preventing an infection of angiotensinogen, angiotensin I (AI), AI analogues, AI fragments and analogues thereof, angiotensin II (AII), AII analogues, AII fragments or analogues thereof or AII AT_2 type 2 receptor agonists.

In another embodiment, the present invention provides improved methods and pharmaceutical compositions for antibiotic therapy, wherein the improvement comprises the administration of an amount effective for treating a bacterial infection

of angiotensinogen, AI, AI analogues, AI fragments and analogues thereof, AII, AII analogues, AII fragments or analogues thereof or AII AT_2 type 2 receptor agonists.

These aspects and other aspects of the invention become apparent in light of the following detailed description.

Brief description of the drawings

Figure 1 is a graph showing the effect of AII on host resistance to bacterial peritonitis, based on the percentage of peritoneal sites without abscesses associated with infection.

Figure 2 is a graph showing the effect of AII on host resistance to bacterial peritonitis, based on the mean overall abscess score.

Figure 3 is a graph showing the effect of AII administration on abscess score (mean score).

Figure 4 is a graph showing the effect of AII administration on abscess score (rank order analysis).

Figure 5 is a graph showing the effect of AII administration on abscess incidence.

Figure 6 is a graph showing the effect of AII with and without Ofloxacin on abscess formation (mean score).

Figure 7 is a graph showing the effect of AII with and without Ofloxacin on abscess formation (rank order).

Figure 8 is a graph showing the effect of AII with and without Ofloxacin on abscess free sites (mean score).

Figure 9 is a graph showing a comparison of AII, AII(1-7) and Neupogen in a rat peritonitis model (mean abscess score).

Figure 10 is a graph showing a comparison of AII, AII(1-7) and Neupogen in a rat peritonitis model (rank order).

Figure 11 is a graph showing a comparison of AII, AII(1-7) and Neupogen in a rat peritonitis model (% abscess free).

Figure 12 is a graph showing a comparison of AII(1-7) analogues in the infection model (mean abscess score).

Figure 13 is a graph showing a comparison of AII(1-7) analogues in the infection model (rank order).

Figure 14 is a graph showing a comparison of AII(1-7) analogues in the infection model (% abscess free).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

All references, patents and patent applications are hereby incorporated by reference in their entirety.

Infections, as used herein, are broadly defined to mean situations when the invasion of a host by an agent is associated with the clinical manifestations of infection including, but not limited to, at least one of the following: abnormal temperature, increased heart rate, abnormal respiratory rate, abnormal white blood cell count, fatigue, chills, muscle ache, pain, dizziness, dehydration, vomiting, diarrhea, and organ dysfunction. Such infections may be bacterial, viral, or parasitic in nature.

U.S. Patent No. 5,015,629 to DiZerega (the entire disclosure of which is hereby incorporated by reference) describes a method for increasing the rate of healing of wound tissue, comprising the application to such tissue of angiotensin II

(AII) in an amount which is sufficient for said increase. The application of AII to wound tissue significantly increases the rate of wound healing, leading to a more rapid re-epithelialization and tissue repair. The term AII refers to an octapeptide present in humans and other species having the sequence Asp-Arg-Val-Tyr-Ile-His-Pro-Phe [SEQ ID NO:1]. The biological formation of angiotensin is initiated by the action of renin on the plasma substrate angiotensinogen (Clouston et al., *Genomics* 2:240-248 (1988); Kageyama et al, *Biochemistry* 23:3603-3609; Ohkubo et al., *Proc. Natl. Acad. Sci.* 80:2196-2200 (1983); each reference hereby incorporated in its entirety). The substance so formed is a decapeptide called angiotensin I (AI) which is converted to AII by the angiotensin converting enzyme (ACE) which removes the C-terminal His-Leu residues from AI [SEQ ID NO: 37]. AII is a known pressor agent and is commercially available.

Studies have shown that AII increases mitogenesis and chemotaxis in cultured cells that are involved in wound repair, and also increases their release of growth factors and extracellular matrices (diZerega, U.S. Patent No. 5,015,629; Dzau et. al., *J. Mol. Cell. Cardiol.* 21:S7 (Supp III) 1989; Berk et. al., *Hypertension* 13:305-14 (1989); Kawahara, et al., *BBRC* 150:52-9 (1988); Naftilan, et al., *J. Clin. Invest.* 83:1419-23 (1989); Taubman et al., *J. Biol. Chem.* 264:526-530 (1989); Nakahara, et al., *BBRC* 184:811-8 (1992); Stouffer and Owens, *Circ. Res.* 70:820 (1992); Wolf, et al., *Am. J. Pathol.* 140:95-107 (1992); Bell and Madri, *Am. J. Pathol.* 137:7-12 (1990). In addition, AII was shown to be angiogenic in rabbit corneal eye and chick chorioallantoic membrane models (Fernandez, et al., *J. Lab. Clin. Med.* 105:141 (1985); LeNoble, et al., Eur. J. Pharmacol. 195:305-6 (1991). Additionally, AII and angiotensin III analogs and fragments thereof have been

shown to be effective in tissue repair. (U.S. Patent No. 5,629,292; International Application No. WO 95/08565; International Application WO 95/08337; International Application No. WO 96/39164; all references hereby incorporated in their entirety.)

Studies have demonstrated that serum levels of ACE are decreased in patients with Adult Respiratory Distress Syndrome (ARDS), which is present in patients with sepsis. (Rice et al., *Circulatory Shock* 11:59-63 (1983), and that ACE levels are increased during recovery of patients with bacterial pneumonia. (Kerttula and Weber, *J. Clin. Pathol.* 39:1250-1253 (1986)) Treatment of mice with an ACE inhibitor, which acts to prevent the formation of AII from its precursor angiotensin I, after thermal injury resulted in greater survival and decreased bacterial translocation compared to controls. (Gennari et al., Shock 6:95-100 (1996))

AII was used to identify changes in pulmonary microcirculation reactivity in a rat model of sepsis. (Kirton et al., *Intensive Care Med.* 18:293-298 (1992)) The effect of AII on the underlying bacterial infection was not addressed. AII has been used in the treatment of septic shock patients as a means to increase system vascular resistance (Thomas et al., *Critical Care Medicine* 19:1084-1086 (1991); Landow J. *Cardiothor. Vasc. Anesth.* 5:97-98 (1991)) with no indication of its effect on the underlying bacterial infection. AII was also used as an adjunct to amrinone treatment of refractory septic shock as a means to reverse the amrinone vasodilatory side effect; the successful treatment of the bacterial infection was attributed entirely to the effect of amrinone. (Ryding et al., *Chest* 107:201-203 (1995).

Based on all of the above, there is no indication in the art that angiotensinogen, AI, AII, AI or AII analogues or fragments or AII AT_2 type 2

receptor agonists would be useful for the treatment and prevention of bacterial, viral, or parasitic infections, or that angiotensinogen, AI, AII, AI or AII analogues or fragments or AII AT_2 type 2 receptor agonists would be useful as an improvement for antibiotic therapy.

A peptide agonist selective for the AT2 receptor (AII has 100 times higher affinity for AT2 than AT1) has been identified. This peptide is p-aminophenylalanine 6-AII ["(p-NH_2-Phe) 6-AII"], Asp-Arg-Val-Tyr-Ile-Xaa-Pro-Phe [SEQ ID NO.36] wherein Xaa is p-NH_2-Phe (Speth and Kim, BBRC 169:997-1006 (1990). This peptide gave binding characteristics comparable to AT2 antagonists in the experimental models tested (Catalioto, et al., *Eur. J. Pharmacol.* 256:93-97 (1994); Bryson, et al., *Eur. J. Pharmacol.* 225:119-127 (1992).

The effects of AII receptor and AII receptor antagonists have been examined in two experimental models of vascular injury and repair which suggest that both AII receptor subtypes (AT1 and AT2) play a role in wound healing (Janiak et al., *Hypertension* 20:737-45 (1992); Prescott, et al., *Am. J. Pathol.* 139:1291-1296 (1991); Kauffman, et al., *Life Sci.* 49:223-228 (1991); Viswanathan, et al., *Peptides* 13:783-786 (1992); Kimura, et al., *BBRC* 187:1083-1090 (1992).

Many studies have focused upon AII(1-7) (AII residues 1-7) or other fragments of AII to evaluate their activity. AII(1-7) elicits some, but not the full range of effects elicited by AII. Pfeilschifter, et al., *Eur. J. Pharmacol.* 225:57-62 (1992); Jaiswal, et al., *Hypertension* 19(Supp. II):II-49-II-55 (1992); Edwards and Stack, *J. Pharmacol. Exper. Ther.* 266:506-510 (1993); Jaiswal, et al., *J. Pharmacol. Exper. Ther.* 265:664-673 (1991); Jaiswal, ct al., *Hypertension* 17:1115-1120 (1991); Portsi, et a., *Br. J. Pharmacol.* 111:652-654 (1994).

As hereinafter defined, a preferred class of AT2 agonists for use in accordance with the present invention comprises angiotensinogen, angiotensin I (AI), AI analogues, AI fragments and analogues thereof, AII, AII analogues, AII fragments or analogues thereof or AII AT_2 type 2 receptor agonists having p-NH-Phe in a position corresponding to a position 6 of AII. In addition to peptide agents, various nonpeptidic agents (e.g., peptidomimetics) having the requisite AT2 agonist activity are further contemplated for use in accordance with the present invention.

The active AII analogues, fragments of AII and analogues thereof of particular interest in accordance with the present invention comprise a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of general

formula I

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7R^8$$

in which R^1 and R^2 together form a group of formula

$$X\text{-}R^A\text{-}R^B\text{-},$$

wherein X is H or a one to three peptide group,

R^A is suitably selected from Asp, Glu, Asn, Acpc (1-aminocyclopentane carboxylic acid), Ala, Me^2Gly, Pro, Bet, Glu(NH_2), Gly, Asp(NH_2) and Suc,

R^B is suitably selected from Arg, Lys, Ala, Orn, Ser(Ac), Sar, D-Arg and D-Lys;

R^3 is selected from the group consisting of Val, Ala, Leu, Lys, norLeu, Ile, Gly, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, Tyr$(PO_3)_2$, Thr, Ser, Ala, homoSer and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R^4 as a terminal Tyr group.

Compounds falling within the category of AT2 agonists useful in the practice of the invention include the AII analogues set forth above subject to the restriction that R^6 is p-NH_2-Phe.

Particularly preferred combinations for R^A and R^B are Asp-Arg, Asp-Lys, Glu-Arg and Glu-Lys. Particularly preferred embodiments of this class include the following: AII, AIII or AII(2-8), Arg-Val-Tyr-Ile-His-Pro-Phe [SEQ ID NO:2]; AII(3-8), also known as des1-AIII or AIV, Val-Tyr-Ile-His-Pro-Phe [SEQ ID NO:3]; AII(1-7), Asp-Arg-Val-Tyr-Ile-His-Pro {SEQ ID NO:4]; AII(2-7). Arg-Val-Tyr-Ile-His-Pro [SEQ ID NO:5]; AII(3-7), Val-Tyr-Ile-His-Pro [SEQ ID NO:6]; AII(5-8), Ile-His-Pro-Phe [SEQ ID NO:7]; AII(1-6), Asp-Arg-Val-Tyr-Ile-His [SEQ ID NO:8]; AII(1-5), Asp-Arg-Val-Tyr-Ile [SEQ ID NO:9]; AII(1-4), Asp-Arg-Val-Tyr [SEQ ID NO:10]; and AII(1-3), Asp-Arg-Val [SEQ ID NO:11]. Other preferred embodiments include: Arg-norLeu-Tyr-Ile-His-Pro-Phe [SEQ ID NO:12] and Arg-Val-Tyr-norLeu-His-Pro-Phe [SEQ ID NO:13]. Still another preferred embodiment encompassed within the scope of the invention is a peptide having the sequence Asp-Arg-Pro-Tyr-Ile-His-Pro-Phe [SEQ ID NO:31]. AII(6-8), His-Pro-Phe [SEQ

ID NO:14] and AII(4-8), Tyr-Ile-His-Pro-Phe [SEQ ID NO:15] were also tested and found not to be effective.

In a particularly preferred embodiment, the active compounds of the present invention are selected from those comprising the following general formula:

Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein

R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu;

R2 is selected from the group consisting of Ala, Tyr, and $Tyr(PO_3)_2$; and

R3 is Phe or is absent.

Another class of compounds of particular interest in accordance with the present invention are those of the general formula II

$$R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8$$

in which R^2 is selected from the group consisting of H, Arg, Lys, Ala, Orn, Ser(Ac), Sar, D-Arg and D-Lys;

R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Ile, Gly, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, $Tyr(PO_3)_2$, Thr, Ser, homoSer and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr.

A particularly preferred subclass of the compounds of general formula II has the formula

R^2-R^3-Tyr-R^5-His-Pro-Phe [SEQ ID NO:16]

wherein R^2, R^3 and R^5 are as previously defined. Particularly preferred is angiotensin III of the formula Arg-Val-Tyr-Ile-His-Pro-Phe [SEQ ID NO:2]. Other preferred compounds include peptides having the structures Arg-Val-Tyr-Gly-His-Pro-Phe [SEQ ID NO:17] and Arg-Val-Tyr-Ala-His-Pro-Phe [SEQ ID NO:18]. The fragment AII(4-8) was ineffective in repeated tests; this is believed to be due to the exposed tyrosine on the N-terminus.

In the above formulas, the standard three-letter abbreviations for amino acid residues are employed. In the absence of an indication to the contrary, the L-form of the amino acid is intended. Other residues are abbreviated as follows:

TABLE 1

Abbreviation for Amino Acids

Me^2Gly	N,N-dimethylglycyl
Bet	1-carboxy-N,N,N-trimethylmethanaminium hydroxide inner salt (betaine)
Suc	Succinyl
Phe(Br)	p-bromo-L-phenylalanyl
azaTyr	aza-α'-homo-L-tyrosyl
Acpc	1-aminocyclopentane carboxylic acid
Aib	2-aminoisobutyric acid
Sar	N-methylglycyl (sarcosine)

It has been suggested that AII and its analogues adopt either a *gamma* or a *beta* turn (Regoli, et al., *Pharmacological Reviews* 26:69 (1974). In general, it is believed that neutral side chains in position R^3, R^5 and R^7 may be involved in maintaining the appropriate distance between active groups in positions R^4, R^6 and R^8 primarily responsible for binding to receptors and/or intrinsic activity. Hydrophobic side chains in positions R^3, R^5 and R^8 may also play an important role in the whole conformation of the peptide and/or contribute to the formation of a hypothetical hydrophobic pocket.

Appropriate side chains on the amino acid in position R^2 may contribute to affinity of the compounds for target receptors and/or play an important role in the conformation of the peptide. For this reason, Arg and Lys are particularly preferred as R^2.

For purposes of the present invention, it is believed that R^3 may be involved in the formation of linear or nonlinear hydrogen bonds with R^5 (in the gamma turn model) or R^6 (in the beta turn model). R^3 would also participate in the first turn in a beta antiparallel structure (which has also been proposed as a possible structure). In contrast to other positions in general formula I, it appears that beta and gamma branching are equally effective in this position. Moreover, a single hydrogen bond may be sufficient to maintain a relatively stable conformation. Accordingly, R^3 may suitably be selected from Val, Ala, Leu, norLeu, Ile, Gly, Pro, Aib, Acpc and Tyr. Lys has also been found to be effective at R^3.

With respect to R^4, conformational analyses have suggested that the side chain in this position (as well as in R^3 and R^5) contribute to a hydrophobic cluster believed to be essential for occupation and stimulation of receptors. Thus, R^4 is

preferably selected from Tyr, Thr, Tyr $(PO_3)_2$, homoSer, Ser and azaTyr. In this position, Tyr is particularly preferred as it may form a hydrogen bond with the receptor site capable of accepting a hydrogen from the phenolic hydroxyl (Regoli, et al. (1974), *supra*). Ala has also been found to be effective at R^4.

In position R^5, an amino acid with a β aliphatic or alicyclic chain is particularly desirable. Therefore, while Gly is suitable in position R^5, it is preferred that the amino acid in this position be selected from Ile, Ala, Leu, norLeu, Gly and Val.

In the angiotensinogen, AI, AI analogues, AI fragments and analogues thereof, AII, AII analogues, fragments and analogues of fragments of particular interest in accordance with the present invention, R^6 is His, Arg or 6-NH_2-Phe. The unique properties of the imidazole ring of histidine (e.g., ionization at physiological pH, ability to act as proton donor or acceptor, aromatic character) are believed to contribute to its particular utility as R^6. For example, conformational models suggest that His may participate in hydrogen bond formation (in the *beta* model) or in the second turn of the antiparallel structure by influencing the orientation of R^7. Similarly, it is presently considered that R^7 should be Pro in order to provide the most desirable orientation of R^8. In position R^8, both a hydrophobic ring and an anionic carboxyl terminal appear to be particularly useful in binding of the analogues of interest to receptors; therefore, Tyr and especially Phe are preferred for purposes of the present invention.

Analogues of particular interest include the following:

TABLE 2

Angiotensin II Analogues

Analogue Name	Amino Acid Sequence	Sequence Identifier
Analogue 1	Asp-Arg-Val-Tyr-Val-His-Pro-Phe	SEQ ID NO: 19
Analogue 2	Asn-Arg-Val-Tyr-Val-His-Pro-Phe	SEQ ID NO: 20
Analogue 3	Ala-Pro-Gly-Asp-Arg-Ile-Tyr-Val-His-Pro-Phe	SEQ ID NO: 21
Analogue 4	Glu-Arg-Val-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 22
Analogue 5	Asp-Lys-Val-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 23
Analogue 6	Asp-Arg-Ala-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 24
Analogue 7	Asp-Arg-Val-Thr-Ile-His-Pro-Phe	SEQ ID NO: 25
Analogue 8	Asp-Arg-Val-Tyr-Leu-His-Pro-Phe	SEQ ID NO: 26
Analogue 9	Asp-Arg-Val-Tyr-Ile-Arg-Pro-Phe	SEQ ID NO: 27
Analogue 10	Asp-Arg-Val-Tyr-Ile-His-Ala-Phe	SEQ ID NO: 28
Analogue 11	Asp-Arg-Val-Tyr-Ile-His-Pro-Tyr	SEQ ID NO: 29
Analogue 12	Pro-Arg-Val-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 30
Analogue 13	Asp-Arg-Pro-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 31
Analogue 14	Asp-Arg-Val-Tyr$(PO_3)_2$-Ile-His-Pro-Phe	SEQ ID NO: 32
Analogue 15	Asp-Arg-norLeu-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 33
Analogue 16	Asp-Arg-Val-Tyr-norLeu-His-Pro-Phe	SEQ ID NO: 34
Analogue 17	Asp-Arg-Val-homoSer-Tyr-Ile-His-Pro-Phe	SEQ ID NO: 35

The polypeptides of the instant invention may be produced by any standard method, including but not limited to recombinant DNA technology and conventional synthetic methods including, but not limited to, those set forth in J. M. Stewart and J. D. Young, *Solid Phase Peptide Synthesis*, 2nd ed., Pierce Chemical Co., Rockford, Ill. (1984) and J. Meienhofer, *Hormonal Proteins and Peptides*, Vol. 2, Academic Press, New York, (1973) for solid phase synthesis and E. Schroder and K. Lubke, *The Peptides*, Vol. 1, Academic Press, New York, (1965) for solution synthesis. The disclosures of the foregoing treatises are incorporated by reference herein.

In general, these methods involve the sequential addition of protected amino acids to a growing peptide chain (U.S. Patent No. 5,693,616, herein incorporated by reference in its entirety). Normally, either the amino or carboxyl group of the first

amino acid and any reactive side chain group are protected. This protected amino acid is then either attached to an inert solid support, or utilized in solution, and the next amino acid in the sequence, also suitably protected, is added under conditions amenable to formation of the amide linkage. After all the desired amino acids have been linked in the proper sequence, protecting groups and any solid support are removed to afford the crude polypeptide. The polypeptide is desalted and purified, preferably chromatographically, to yield the final product.

Preferably, peptides are synthesized according to standard solid-phase methodologies, such as may be performed on an Applied Biosystems Model 430A peptide synthesizer (Applied Biosystems, Foster City, Calif.), according to manufacturer's instructions. Other methods of synthesizing peptides or peptidomimetics, either by solid phase methodologies or in liquid phase, are well known to those skilled in the art.

In one aspect, the present invention provides methods and kits for treating and preventing infections in a mammal comprising administering to the mammal an amount effective to treat or prevent an infection of angiotensinogen, angiotensin I (AI), AI analogues, AI fragments and analogues thereof, angiotensin II (AII), AII analogues, AII fragments or analogues thereof or AII AT_2 type 2 receptor agonists (the active agents).

The invention is appropriate for the treatment and prevention of all types of infection, including but not limited to septic shock, peritonitis, bacteremia, endotoxemia, and viral and parasitic infections. The methods of the invention are applicable to infections resulting from any condition, including but not limited to

wounds, burns, infected intravenous catheters, trauma, ulcerations, gastrointestinal obstructions, or due to the immuno-compromised state of the host.

The active agents of the invention can be used alone or in a combination of active agents, or may be used in combination with other anti-infective agents, including but not limited to oflaxacin, granulocyte colony stimulating factors, gentamicin, augmentin or cephalosporins such as ceftazidime, amino-glycosides (such as amikacin, tobramycin, netilmicin, and gentamicin), related beta-lactam agents such as maxalactam, carbopenems such as imipenem, monobactam agents such as aztreonam; ampicillin and broad-spectrum penicillins, (e.g., penicillinase-resistant penicillins, ureidopenicillins or antipseudomonal penicillin or Augmentin) that are active against P. aeruginosa, Enterobacter species, indole-positive Proteus species, and Serratia. Also included within the definition of anti-infective agents are antifungal agents, amphotericin and the like as well as anti-vital agents such as famvir and acyclovir.

In another embodiment, the present invention provides improved methods, compositions, and kits for antibiotic therapy, wherein the improvement comprises the administration of an amount effective for treating a bacterial infection of the active agents.

The active agents may be administered by any suitable route, including orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intraarterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally.

The active agents may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The compounds of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the peptide, and are not harmful for the proposed application. In this regard, the compounds of the present invention are very stable but are hydrolyzed by strong acids and bases. The compounds of the present invention are soluble in organic solvents and in aqueous solutions at pH 5-8.

The active agents may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. For administration, the active agents are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

The dosage regimen for treating or preventing infections in a mammal with the active agents is based on a variety of factors, including the type of injury, the age, weight, sex, medical condition of the individual, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods. Dosage levels of the order of between 0.1 ng/kg and 10 mg/kg body weight active agent are useful for all methods of use disclosed herein.

The treatment regime will also vary depending on the infection being treated, based on a variety of factors, including the type of infection, the age, weight, sex, medical condition of the individual, the severity of the condition, the route of administration, and the particular compound employed. For example, the active agents are administered to a mammal suffering from bacteremia for two weeks. The therapy is administered for between two and five times per day at dosages as described above.

In a preferred embodiment, the active agent is administered subcutaneously or intraperitoneally. A suitable subcutaneous dose of active agent is preferably between about 0.1 ng/kg and about 10 mg/kg administered twice daily for a time sufficient to treat or prevent infections in a mammal. In a more preferred embodiment, the concentration of active agent is between about 100 ng/kg body weight and about 10.0 mg/kg body weight. In a most preferred embodiment, the

concentration of active agent is between about 10 μg/kg body weight and about 10.0 mg/kg body weight. This dosage regimen maximizes the therapeutic benefits of the subject invention while minimizing the amount of antagonist needed. Such an application minimizes costs as well as possible deleterious side effects.

For subcutaneous administration, the active ingredient may comprise from 0.0001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

In another preferred embodiment of the present invention, the active agent is administered topically. Suitable topical doses and active ingredient concentration in the formulation are as described for subcutaneous administration.

In a further aspect, the present invention provides kits for treating or preventing infection in a mammal, wherein the kits comprise an effective amount of the active agents for treating or preventing infection in a mammal, and instructions for using the amount effective of active agent as a therapeutic. In a preferred embodiment, the kit further comprises a pharmaceutically acceptable carrier, such as those adjuvants described above. In another preferred embodiment, the kit further comprises a means for delivery of the active agent to a patient. Such devices include, but are not limited to syringes, matrical or micellar solutions, bandages, wound dressings, aerosol sprays, lipid foams, transdermal patches, topical administrative agents, polyethylene glycol polymers, carboxymethyl cellulose preparations, crystalloid preparations (e.g., saline, Ringer's lactate solution, phosphate-buffered saline, etc.), viscoelastics, polyethylene glycols, and polypropylene glycols. The means for delivery may either contain the effective

amount of the active agent, or may be separate from the active agents, which are then applied to the means for delivery at the time of use.

The active agents can be administered alone, or may be combined with other anti-infective agents in combinatorial therapy. In a preferred embodiment the anti-infective agent is selected from the group consisting of Ofloxacin and granulocyte colony stimulating factors.

In another aspect of the invention, the method comprises pharmaceutical compositions for treating or preventing infections, comprising the active agents of the invention, an amount an amount effective to treat or prevent an infection of an anti-infective agent and a pharmaceutically acceptable carrier. In a preferred embodiment, the anti-infective agent is select4ed from the group consisting of Ofloxacin and granulocyte colony stimulating factors.

The methods and kits of the present invention provide significant benefits for the treatment and prophylaxis of mammalian infections. The methods and kits of the present invention may be particularly valuable in the hospital setting, where potentially serious bacterial infections are common, and may also enable decreased reliance on high doses of antibiotics, which can lead to the development of antibiotic resistant bacteria.

The present invention may be better understood with reference to the accompanying example that is intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

Example 1 AII effect in a rat model of bacterial peritonitis

The following rat model of bacteremia was used in all subsequent examples. Forty-five female Sprague Dawley rats, weighing between 175 and 225 grams each, were used in the study. Fifteen of the rats were used to produce fecal material. The rats were housed in the University of Southern California vivarium on a 12:12 hour light/dark cycle and were quarantined at least two days prior to surgery. Food and water were available ad libitum except in the immediate postoperative period.

AII was purchased from Bacem (Torrance, CA) and resuspended in saline on the day of surgery. The peptide was placed in an Alzet miniosmotic pump (Model 1002, 0.5 µl/hour for 14 days). The cecal contents and feces from rats fed hamburger for two weeks were collected and mixed 1:1 with peptone yeast glucose broth (Scott Laboratories) and 10% barium sulfate. The amount of this fecal preparation that caused mortality in 0 to 30% of the rats (LD_{20}) was determined in preliminary studies. The appropriate amount of material was added to a gelatin capsule (Number 1, Eli Lilly Co., Indianapolis, IN). This capsule was then placed in a second larger capsule (Number 00, Eli Lilly Co.) This was referred to as a double-walled gelatin capsule.

The rats underwent a standardized procedure for laparotomy (intramuscular anesthesia with ketamine/rompum, shaving with animal clippers, betadine scrub, alcohol scrub). A 2 cm incision was then made on the midline. A double-walled gelatin capsule was placed on the right side of the abdomen through the incision. A polyethylene tube (PE 60) was sutured to the left sidewall and attached to the Alzot miniosmotic pump containing either saline, 10 µg/kg/day AII, or 100 µg/kg/day AII. The pump was then placed in a subcutaneous pocket. The abdominal wall and skin was then sutured closed using two layers of 4-0 Ethilon suture. Following surgery,

the rats received analgesic for three days and were observed twice daily for signs of morbidity and mortality.

Rats that died during the 11 day post-operative observation period were necropsied to confirm the presence of an acute bacterial infection. The rats that survived the initial acute infection were terminated on day 12 after surgery. Each rat was examined for odor upon opening and splenomegaly. Additionally, four areas of the peritoneum were examined for abscess formation. These areas included the liver, abdominal wall, bowel and omentum. The abscesses were scored at each site as follows:

0	No abscess present at site
0.5	One very small abscess present at site
1	Several small abscesses present at site
2	Medium abscess present at site
3	Large or several medium abscesses present at site
4	One very large or several small abscesses present at site

The scoring was conducted in a blinded fashion by two separate observers and the scores recorded. If there was a disagreement between the two observers as to the score at a particular site the more severe score was reported. The results (Figures 1-2 and Tables 3-5) demonstrate that although AII administration did not affect mortality after exposure to the bacterial inoculum, it did reduce the formation of abscesses associated with the infection.

Table 3 Abscess Scores in Saline Treated Rats

Liver	Sidewall	Bowel	Omentum	Overall
2	2	2	2	8
2	4	0	2	8
0	4	2	4	10
2	4	0	3	9
3	3	3	3	12
3	3	0	3	9
2	0	0	2	4

3	3	3	0	9
3	3	0	3	9
2	2	0	2	6

Table 4 Abscess Scores in Rats Treated with 10 µg/kg/day AII

Liver	Sidewall	Bowel	Omentum	Overall
0	0	1	1	2
2	2	0	2	6
0	0	0	2	2
0	0	3	1	4
2	0	0	2	4
0	0	0	1	1
0	2	0	0	2
0	1	0	2	3

Table 5 Abscess Scores in Rats Treated with 100 µg/kg/day AII

Liver	Sidewall	Bowel	Omentum	Overall
0	0	0	0	0
0	0	0	0	0
0	0	0	1	1
0	0	0	2	2
0	0	0	1	1
0	0	0	1	1
0	1	0	1	2
0	0	0	0	0
0	0	1	0	1

5

Example 2. AII administration timing and route

The rat peritonitis model was generated as in Example 1. AII (100 µg/kg/day) was given either: (1) subcutaneously (daily) three days before and after initiation of infection (SQ/SQ); (2) subcutaneously only after initiation of infection 10 (SQ Post); (3) subcutaneously (daily) three days before and intraperitoneally after initiation of infection (SQ/IP); (4) intraperitoneally only after initiation of infection (IP Post); or (5) intraperitoneally via Alzet pump starting at the initiation of infection throughout the post-infection interval (Pump).

The results of these experiments are expressed in three different ways. The first is the mean of the overall abscess scores in the abdomen of the animals (FIG. 3: Mean Score). These data are nonparametric and should therefore be analyzed by a nonparametric statistical test. We used an analysis of variance of the rank order of the overall abscess scores; thus, the second method of presenting data is as the mean and SEM of the rank (FIG. 4: Rank Order Analysis). Lastly, it is important to determine whether the test compounds reduce the incidence of abscesses in addition to reducing abscess size. Therefore, the incidence of abscess free sites (FIG. 5: % Sites Abscess Free) is also graphically presented.

The data for these experiments are presented in Figure 3-5. These data indicate that a reduction in both the size and the occurrence of abscess formation (ie: reduced bacterial peritonitis) was observed after each treatment regimen. Thus, the data indicate that AII is effective both for treating and preventing bacterial peritonitis.

Example 3. Effect of AII compared to and in combination with Ofloxacin

The rat peritonitis model was generated as in Example 1. AII (100 µg/kg/day) was give alone or in combination (AII/Oflox) with Ofloxacin (Sigma Chemical CO., St. Loius, MO) (6.7 mg/kg/day), a broad spectrum antibiotic. Pretreatment with AII by subcutaneous injection was given to all animals that received post-infection AII for three days. The routes of administration tested included subcutaneous (sq) and intraperitoneal via Alzet miniosmotic pump (Pump). Experimental results are presented as described for example 2. The results

demonstrated that AII treatment provided improved reduction in the size and the occurrence of abscess formation (ie: reduced occurrence and severity of bacterial peritonitis) relative to Ofloxacin. Furthermore, combined therapy with AII and Ofloxacin improved the efficacy of the Ofloxacin. (FIGURES 6-8)

Example 4. Comparison of AII, AII(1-7) and G-CSF

The rat peritonitis model was generated as in Example 1. AII (1-100 µg/kg/day) and AII(1-7) (1-100 µg/kg/day) treatment were compared with G-CSF treatment (Neupogen--Amgen, Thousand Oaks, CA) (0.1-10 µg/kg/day) for reduction in abscess size and occurrence. The experimental treatments were given by subcutaneous injection starting three days prior to initiation of infection and continued until the animals were euthanized.

Experimental results are presented as described for example 2. The results demonstrated that at all concentrations tested, treatment with both AII and AII(1-7) provided improved reduction in the size and the occurrence of abscess formation (ie: reduced occurrence and severity of bacterial peritonitis) relative to G-CSF treatment. (Figures 9-11)

Example 5. AII(1-7) analogue effect on abscess formation

The rat peritonitis model was generated as in Example 1. Subcutaneous injections with the peptides listed in Table 6 (10-100 µg/kg/day) were initiated three days prior to the initiation of infection and continued until the animals were euthanized.

Experimental results are presented as described for example 2. The results demonstrated that at all concentrations tested, treatment with each of the AII(1-7) analogues reduced the size and occurrence of abscess formation (ie: reduced occurrence and severity of bacterial peritonitis). (Figures 12-14)

Table 6 AII(1-7) Analogues used

Peptide	Designation	Sequence	SEQ ID NO
1GD	Ala4-AII(1-7)	DRVAIHP	SEQ ID NO:38
2GD	Pro3-AII(1-7)	DRPYIHP	SEQ ID NO:39
5GD	Lys3-AII(1-7)	DRKYIHP	SEQ ID NO:40
9GD	NorLeu-AII(1-7)	DR(nor)YIHP	SEQ ID NO:41
AII		DRVYIHPF	SEQ ID NO:1

It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact compounds, compositions, methods, procedures or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

We claim:

1. A method for treating or preventing an infection in a mammal comprising administering to a mammal suffering from an infection an amount effective to treat or prevent an infection of at least one active agent comprising a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of general formula I

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7R^8$$

in which R^1 and R^2 together form a group of formula

$$X\text{-}R^A\text{-}R^B\text{-},$$

wherein X is H or a one to three peptide group,

R^A is suitably selected from Asp, Glu, Asn, Acpc (1-aminocyclopentane carboxylic acid), Ala, Me^2Gly, Pro, Bet, Glu(NH_2), Gly, Asp(NH_2) and Suc,

R^B is suitably selected from Arg, Lys, Ala, Orn, Ser(Ac), Sar, D-Arg and D-Lys;

R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Lys, Ile, Gly, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, Tyr(PO_3)$_2$, Thr, Ser, homoSer, Pro, Ala and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R^4 as a terminal Tyr group.

2. The method of claim 1 wherein the active agent is selected from the group consisting of angiotensinogen, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO: 32, SEQ ID NO:33, SEQ ID NO: 34; SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

3. The method of claim 1 wherein the infection comprises a bacterial infection.

4. A kit for treating an infection in a mammal, comprising:

(a) an amount effective to treat or prevent an infection in a mammal of at least one active agent comprising a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of general formula I

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8$$

in which R^1 and R^2 together form a group of formula

$$X\text{-}R^A\text{-}R^B\text{-},$$

wherein X is H or a one to three peptide group,

R^A is suitably selected from Asp, Glu, Asn, Acpc (1-aminocyclopentane carboxylic acid), Ala, Me^2Gly, Pro, Bet, Glu(NH_2), Gly, Asp(NH_2) and Suc,

R^B is suitably selected from Arg, Lys, Ala, Orn, Ser(Ac), Sar, D-Arg and D-Lys;

R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Lys, Ile, Gly, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, Tyr$(PO_3)_2$, Thr, Ser, homoSer, Pro, Ala and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R^4 as a terminal Tyr group.

(b) instructions for using the amount effective of active agent for treating or preventing an infection in a mammal.

5. The kit of claim 4 wherein the active agent is selected from the group consisting of angiotensinogen, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO: 32, SEQ ID NO:33, SEQ ID NO: 34; SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41.

6. The kit of claim 4, further comprising a means for delivery of the active agent.

7. The kit of claim 4 wherein the infection comprises a bacterial infection.

8. An improved method for antibiotic therapy, wherein the improvement comprises the administration to a mammal suffering from a bacterial infection an amount effective to treat bacterial infection of at least one active agent comprising a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of general formula I

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7R^8$$

in which R^1 and R^2 together form a group of formula

$$X\text{-}R^A\text{-}R^B\text{-},$$

wherein X is H or a one to three peptide group,

R^A is suitably selected from Asp, Glu, Asn, Acpc (1-aminocyclopentane carboxylic acid), Ala, Me^2Gly, Pro, Bet, Glu(NH_2), Gly, Asp(NH_2) and Suc,

R^B is suitably selected from Arg, Lys, Ala, Orn, Ser(Ac), Sar, D-Arg and D-Lys;

R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Lys, Ile, Gly, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, Tyr(PO_3)$_2$, Thr, Ser, homoSer, Pro, Ala and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R^4 as a terminal Tyr group.

9. The method of claim 8 wherein the active agent is selected from the group consisting of angiotensinogen, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO: 32, SEQ ID NO:33, SEQ ID NO: 34; SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41.

10. A method for treating or preventing an infection in a mammal comprising administering to the mammal suffering from an infection an amount effective to treat or prevent an infection of at least one active agent comprising a sequence consisting of the following general formula:

Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein

R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu;

R2 is selected from the group consisting of Ala, Tyr, and $Tyr(PO_3)_2$; and

R3 is Phe or is absent.

11. The method of claim 10 wherein the active agent is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

12, The method of claim 10 wherein the infection comprises a bacterial infection.

13. A kit for preventing or treating an infection in a mammal, comprising:

(a) an amount effective to treat or prevent an infection in a mammal of at least one active agent comprising a sequence consisting of at least one active agent comprising a sequence consisting of the following general formula:

Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein

R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu;

R2 is selected from the group consisting of Ala, Tyr, and $Tyr(PO_3)_2$; and

R3 is Phe or is absent; and

(b) instructions for using the amount effective of active agent for treating or preventing an infection in a mammal.

14. The kit of claim 13 wherein the active agent is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

15. The kit of claim 13, further comprising a means for delivery of the active agent.

16. The kit of claim 13 wherein the infection comprises a bacterial infection.

17. An improved method for antibiotic therapy, wherein the improvement comprises the administration to a mammal suffering from a bacterial infection an

amount effective to treat bacterial infection of at least one active agent comprising a sequence consisting of the following general formula:

Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein

R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu;

R2 is selected from the group consisting of Ala, Tyr, and $Tyr(PO_3)_2$; and

R3 is Phe or is absent.

18. The method of claim 17 wherein the active agent is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

19. A pharmaceutical composition for use in treating or preventing an infection comprising

(a) an amount effective to treat or prevent an infection of at least one active agent comprising a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of general formula I

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7R^8$$

in which R^1 and R^2 together form a group of formula

$$X\text{-}R^A\text{-}R^B\text{-},$$

wherein X is H or a one to three peptide group and a peptide bond between R^A and R^B is labile to aminopeptidase A cleavage;

R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Ile, Gly, Lys, Pro, Aib, Acpc and Tyr;

R^4 is selected from the group consisting of Tyr, $Tyr(PO_3)_2$, Thr, Pro, Ser, homoSer and azaTyr;

R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;

R^6 is His, Arg or 6-NH_2-Phe;

R^7 is Pro or Ala; and

R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R^4 as a terminal Tyr group;

(b) an amount effective to treat or prevent an infection of an anti-infective agent; and

(c) a pharmaceutically acceptable carrier.

20. The pharmaceutical composition of claim 19 wherein the active agent is selected from the group consisting of angiotensinogen, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO: 32, SEQ ID NO:33, SEQ ID NO: 34; SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41.

21. The pharmaceutical composition of claim 19 wherein the anti-infective agent is selected from the group consisting of Ofloxacin and granulocyte colony stimulating factors.

22. A pharmaceutical composition for use in treating or preventing an infection comprising

(a) an amount effective to treat or prevent an infection of at least one active agent comprising a sequence consisting of at least three contiguous amino acids of groups R^1-R^8 in the sequence of the following general formula:

Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein

R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu;

R2 is selected from the group consisting of Ala, Tyr, and Tyr$(PO_3)_2$; and

R3 is Phe or is absent;

(b) an amount effective to treat or prevent an infection of an anti-infective agent; and

(c) a pharmaceutically acceptable carrier

23. The pharmaceutical composition of claim 22 wherein the active agent is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

24. The pharmaceutical composition of claim 22 wherein the anti-infective agent is selected from the group consisting of Ofloxacin and granulocyte colony stimulating factors.

25. A kit for preventing or treating an infection in a mammal, comprising:

(a) the pharmaceutical composition of claim 19; and

(b) instructions for using the pharmaceutical composition of claim 19 for treating or preventing an infection in a mammal.

26. A kit for preventing or treating an infection in a mammal, comprising:

(a) the pharmaceutical composition of claim 22; and

(b) instructions for using the pharmaceutical composition of claim 22 for treating or preventing an infection in a mammal.

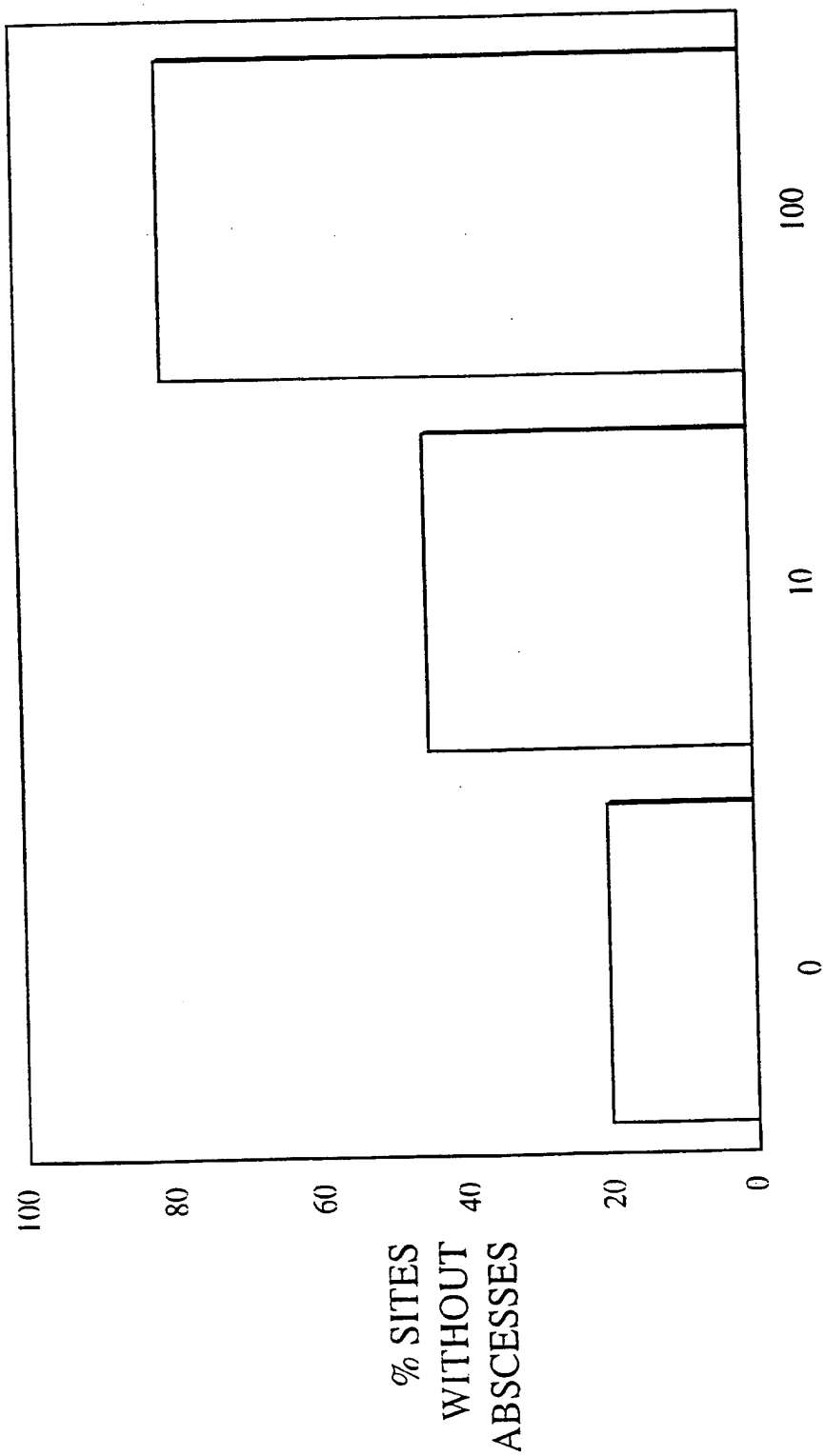


FIG. 1

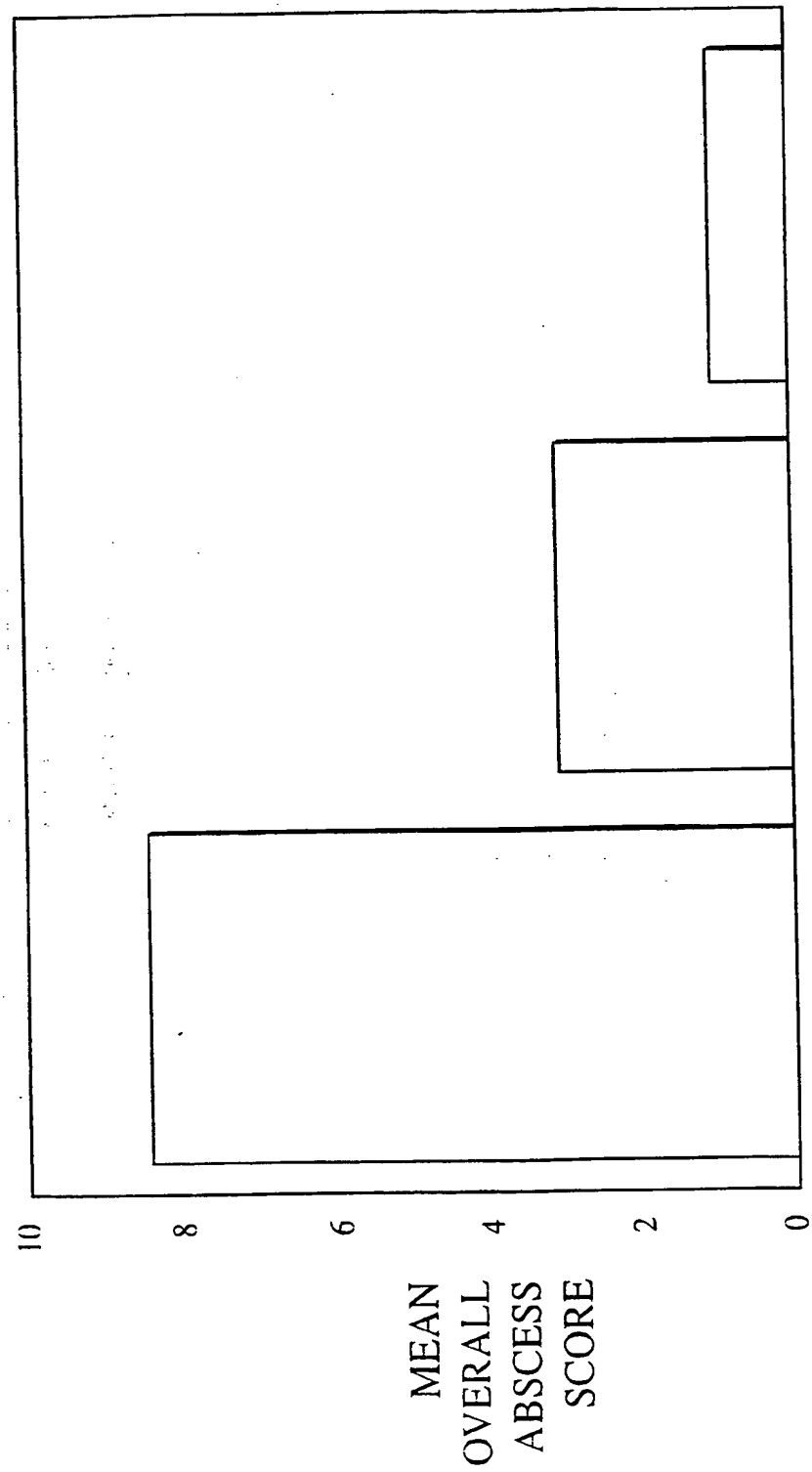
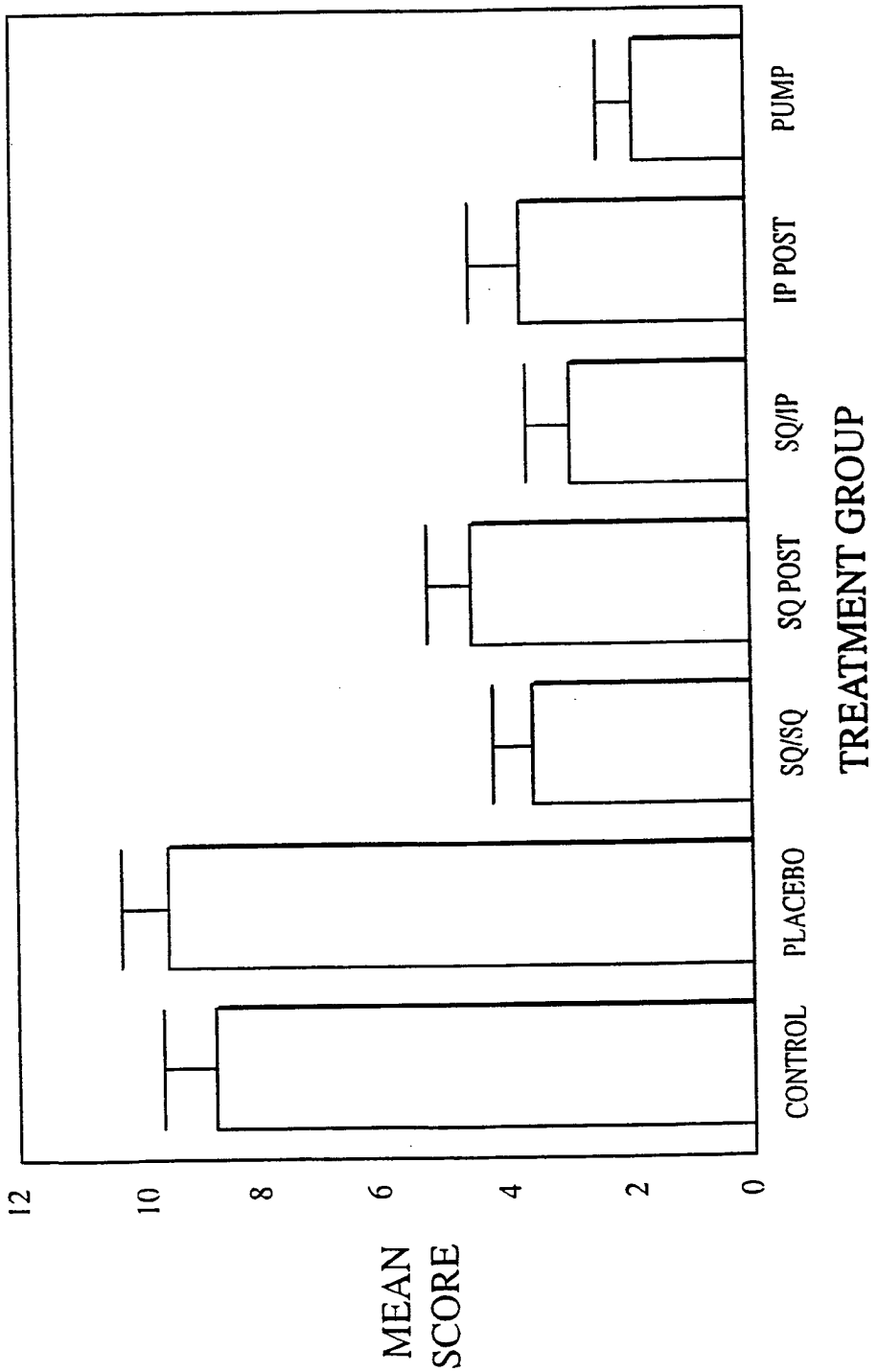


FIG. 2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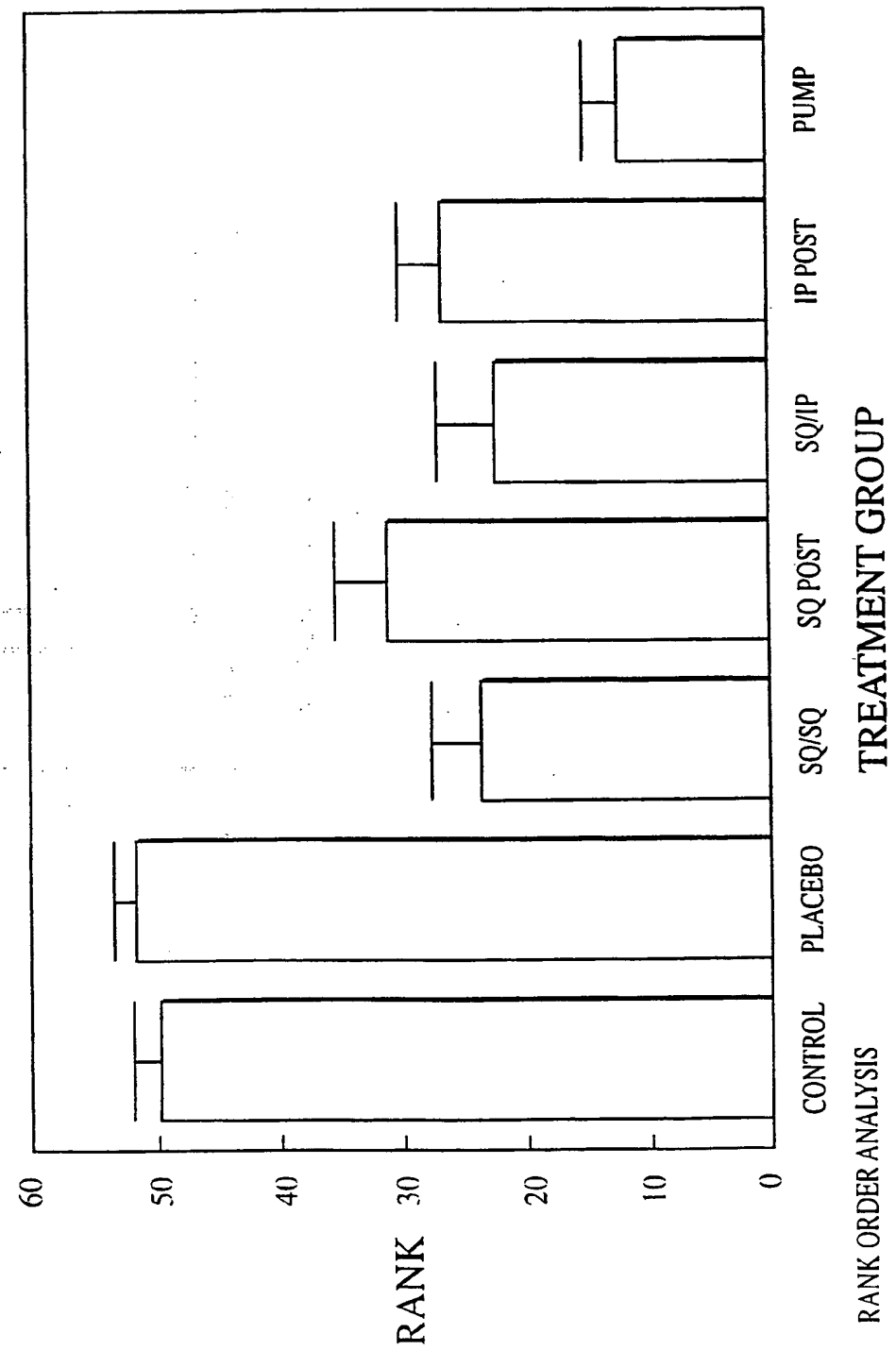
8
10
12
CONTROL
PLACEBO
SQ/SQ
SQ POST
SQ/IP
IP POST
PUMP
TREATMENT GROUP

FIG. 3


RANK ORDER ANALYSIS
RANK
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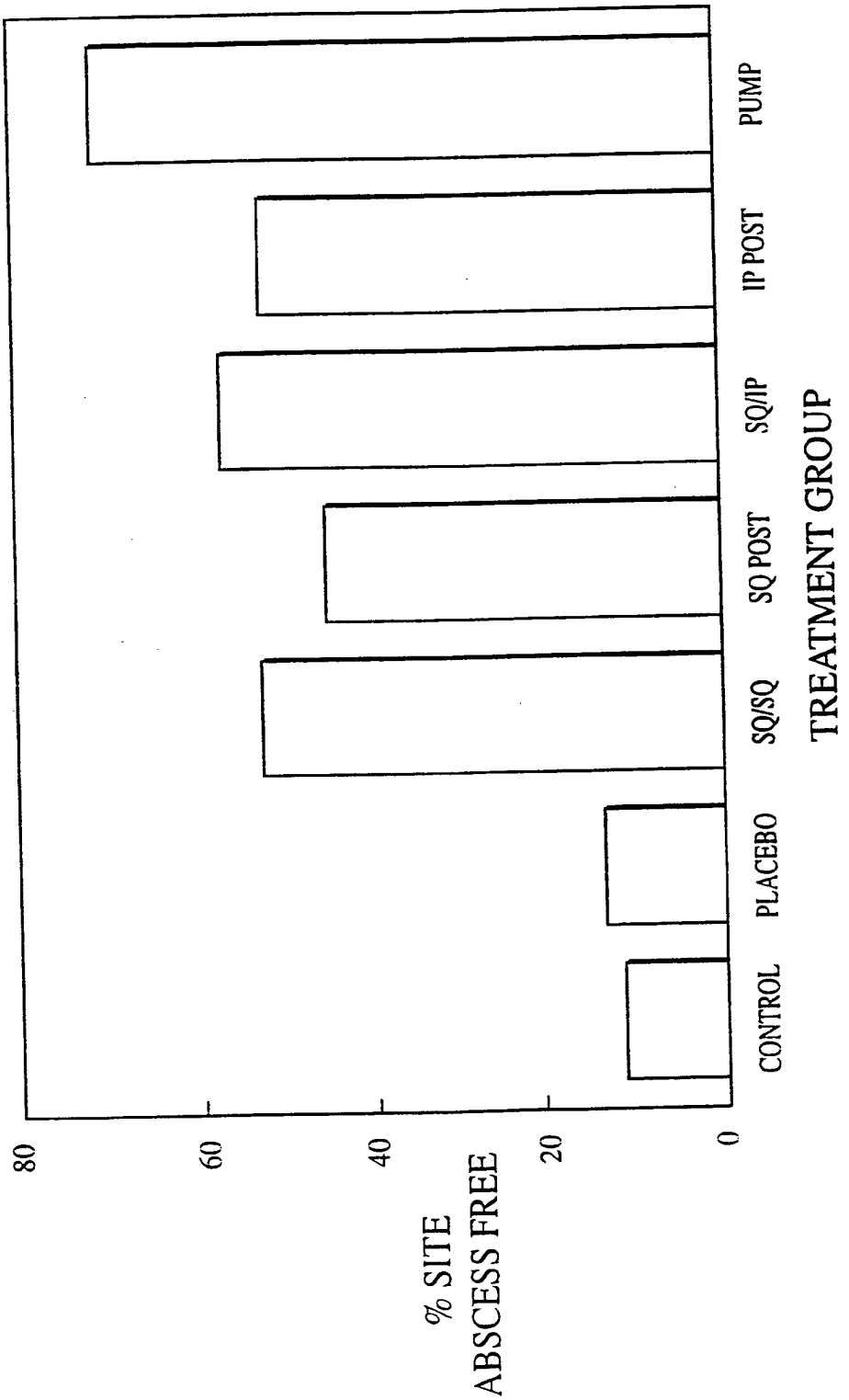
CONTROL
PLACEBO
SQ/SQ
SQ POST
SQ/IP
IP POST
PUMP
TREATMENT GROUP

FIG. 4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40
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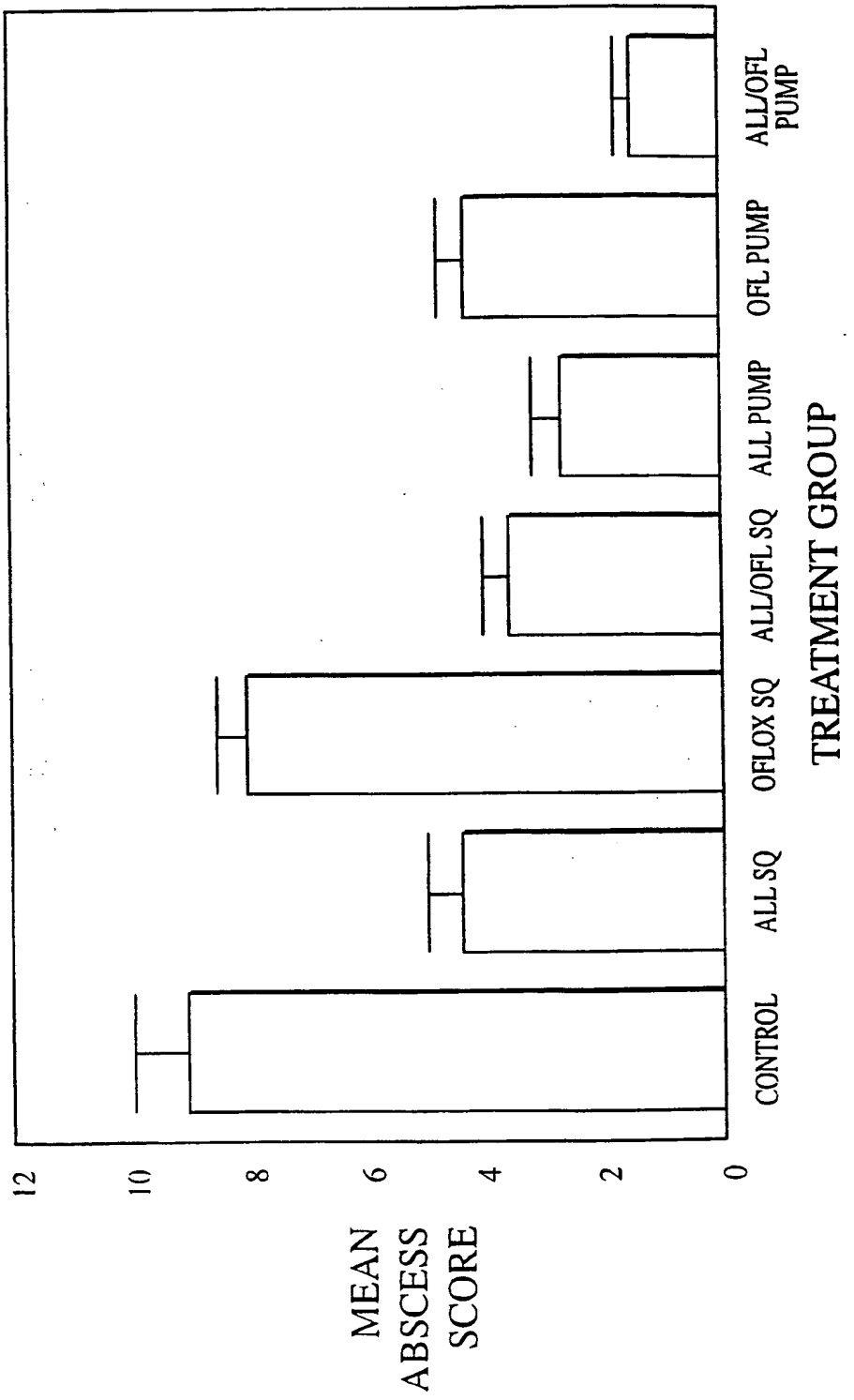
% SITE
ABSCESS FREE
CONTROL
PLACEBO
SQ/SQ
SQ POST
SQ/IP
IP POST
PUMP
TREATMENT GROUP

FIG. 5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2
4
6
8
10
12
CONTROL
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OFLOX SQ
ALL/OFL SQ
ALL PUMP
OFL PUMP
ALL/OFL PUMP
TREATMENT GROUP

FIG. 6

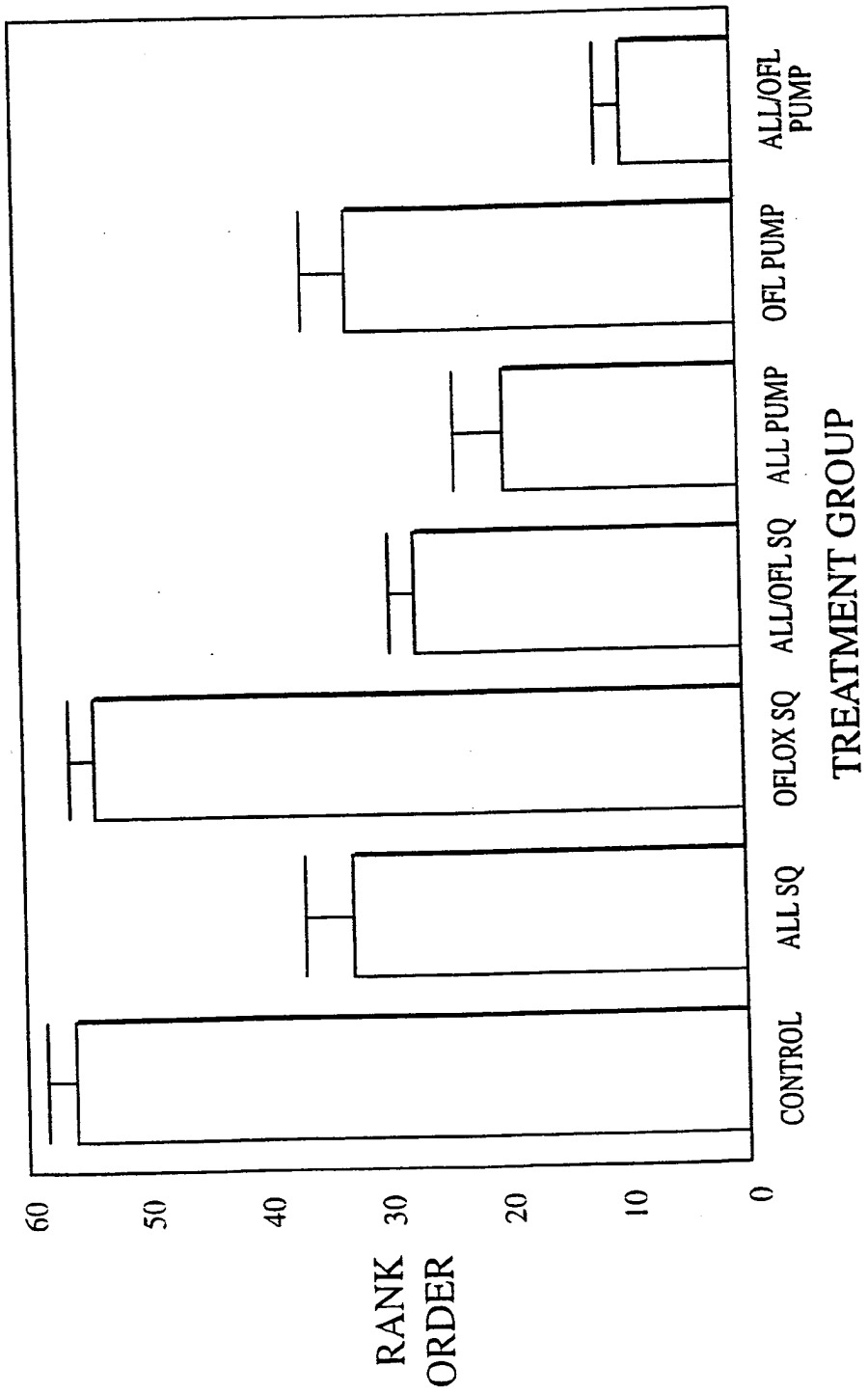

RANK ORDER
60
50
40
30
20
10
0
CONTROL
ALL SQ
OFLOX SQ
ALL/OFL SQ
ALL PUMP
OFL PUMP
ALL/OFL PUMP
TREATMENT GROUP

FIG. 7

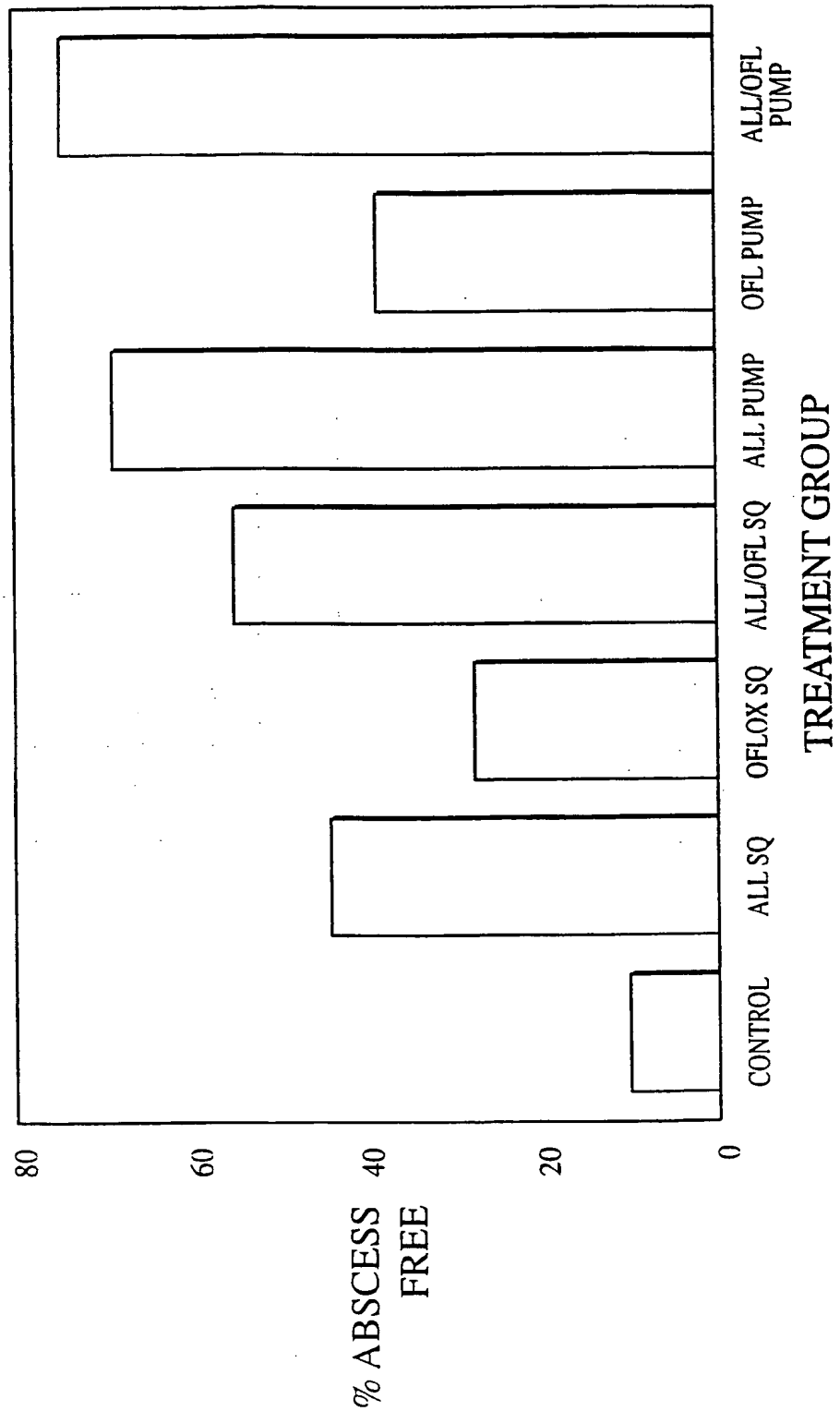
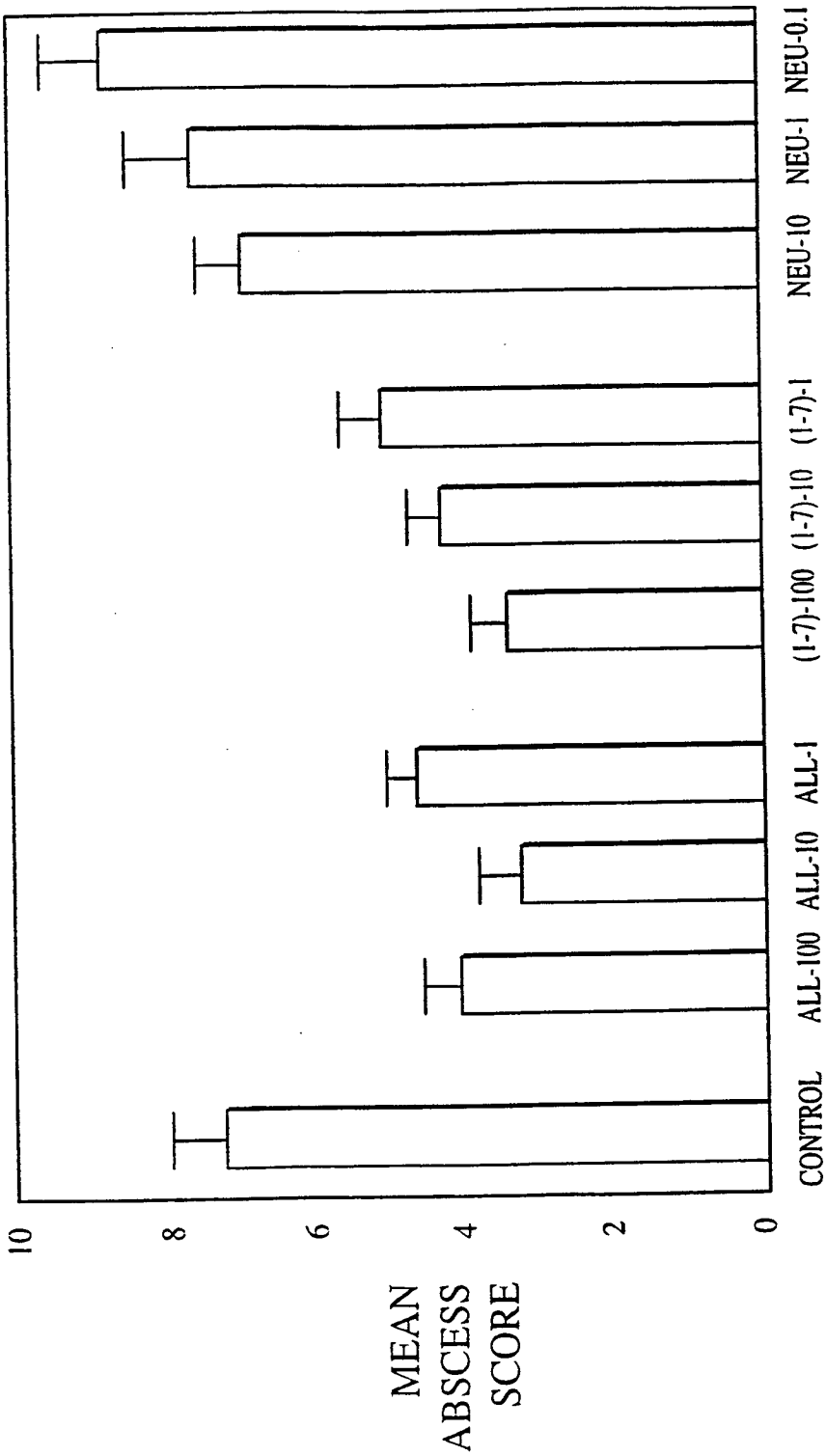

% ABSCESS FREE
0
20
40
60
80
CONTROL
ALL SQ
OFLOX SQ
ALL/OFL SQ
ALL PUMP
OFL PUMP
ALL/OFL PUMP
TREATMENT GROUP

FIG. 8


MEAN ABSCESS SCORE
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2
4
6
8
10
CONTROL
ALL-100
ALL-10
ALL-1
(1-7)-100
(1-7)-10
(1-7)-1
NEU-10
NEU-1
NEU-0.1
TREATMENT GROUPS (µg/kg)

FIG. 9

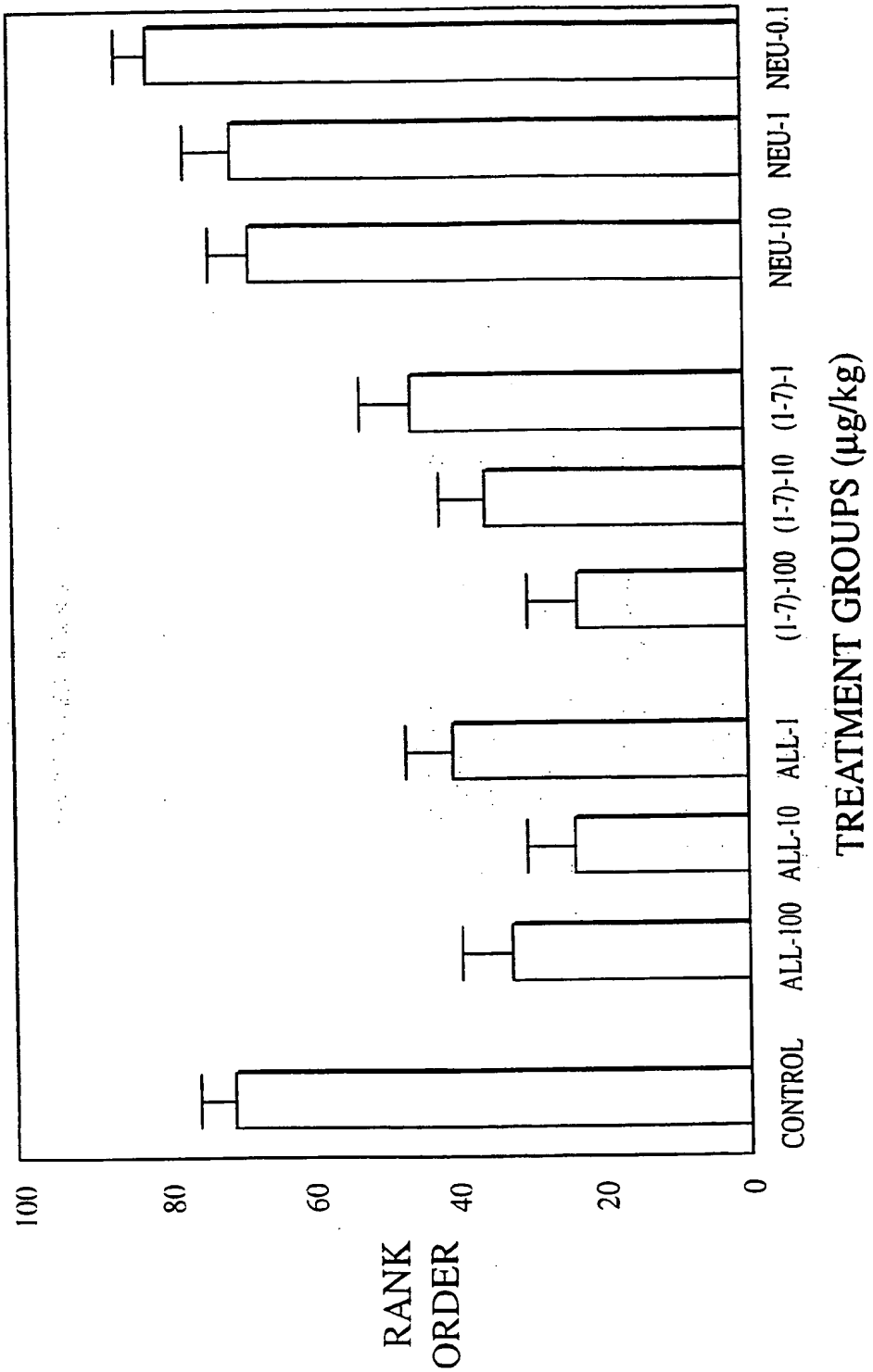
RANK ORDER
100
80
60
40
20
0
CONTROL
ALL-100
ALL-10
ALL-1
(1-7)-100
(1-7)-10
(1-7)-1
NEU-10
NEU-1
NEU-0.1
TREATMENT GROUPS (µg/kg)

FIG. 10

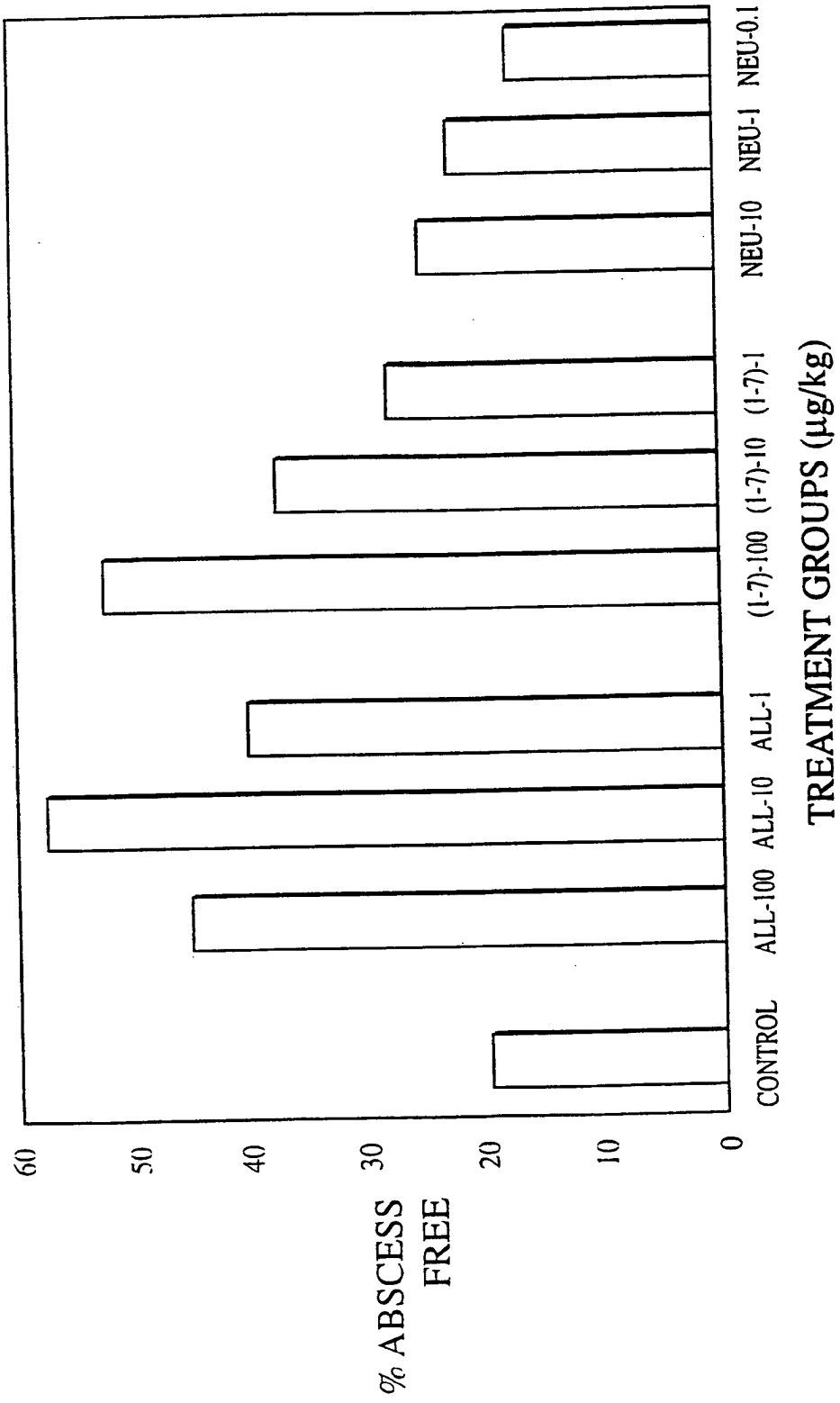
% ABSCESS FREE
60
50
40
30
20
10
0
CONTROL
ALL-100
ALL-10
ALL-1
(1-7)-100
(1-7)-10
(1-7)-1
NEU-10
NEU-1
NEU-0.1
TREATMENT GROUPS (µg/kg)

FIG. 11

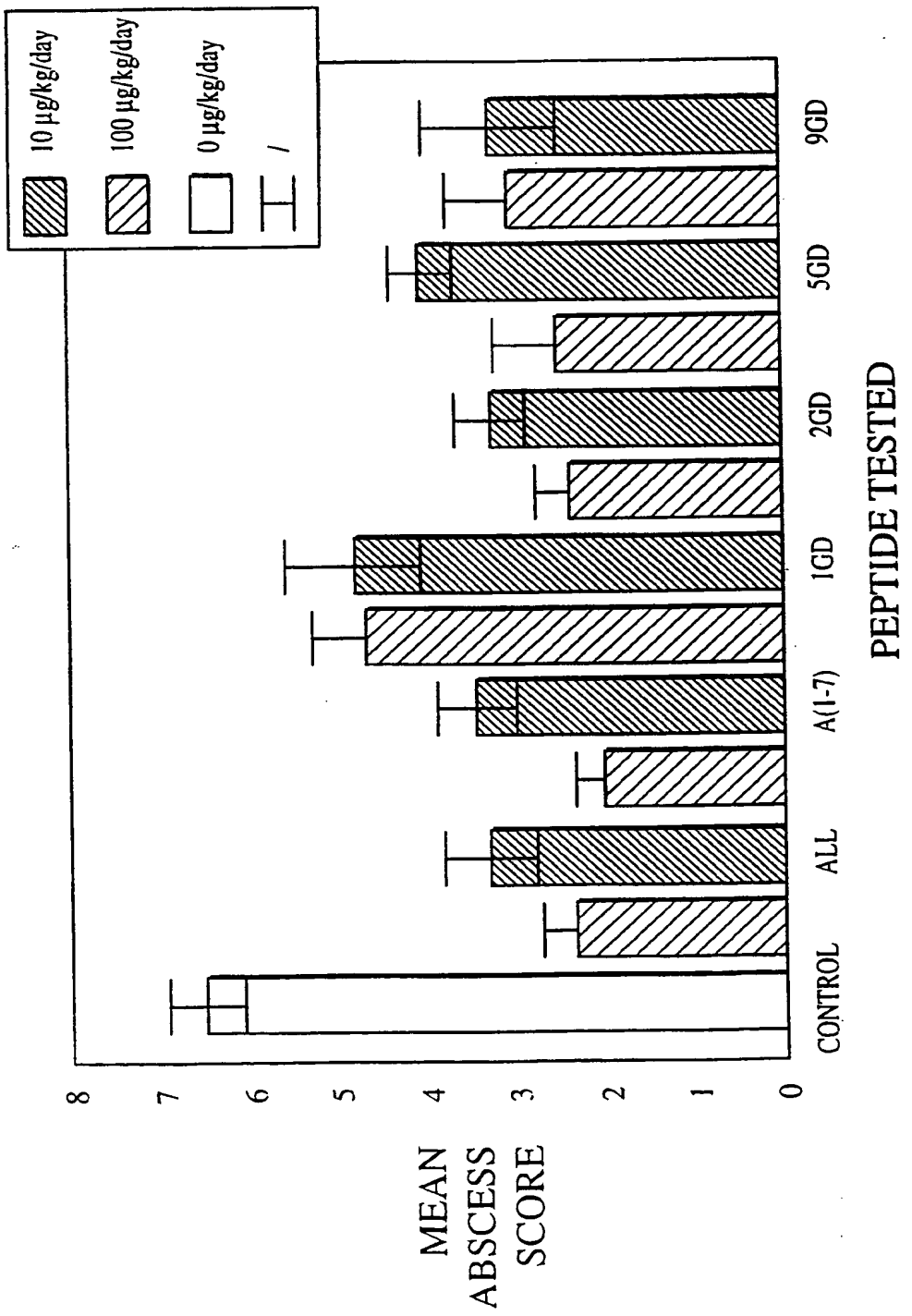
10 µg/kg/day
100 µg/kg/day
0 µg/kg/day
MEAN ABSCESS SCORE
0
1
2
3
4
5
6
7
8
CONTROL
ALL
A(1-7)
1GD
2GD
5GD
9GD
PEPTIDE TESTED

FIG. 12

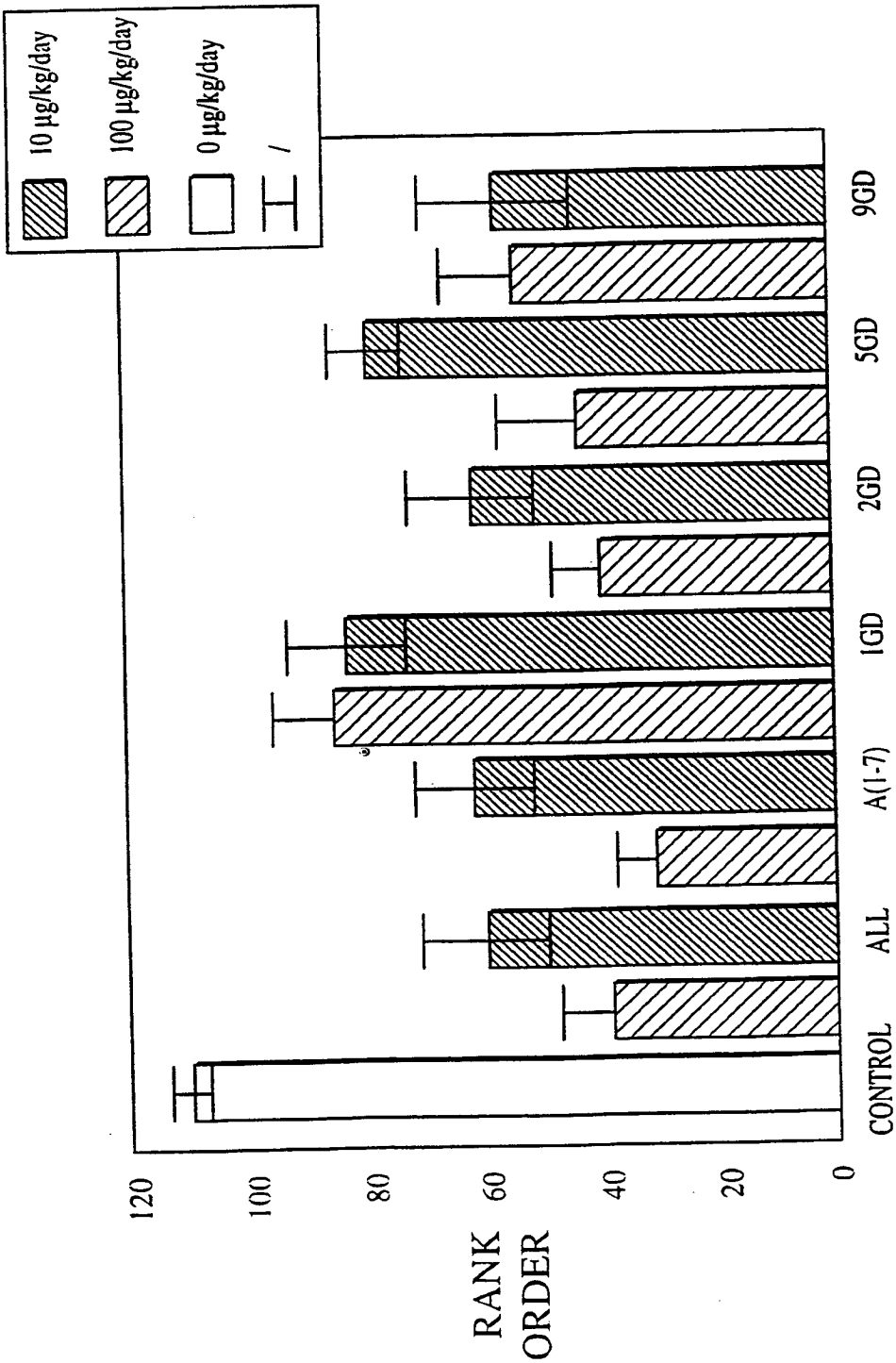
10 µg/kg/day
100 µg/kg/day
0 µg/kg/day
/
RANK ORDER
120
100
80
60
40
20
0
CONTROL
ALL
A(1-7)
1GD
2GD
5GD
9GD
PEPTIDE TESTED

FIG. 13

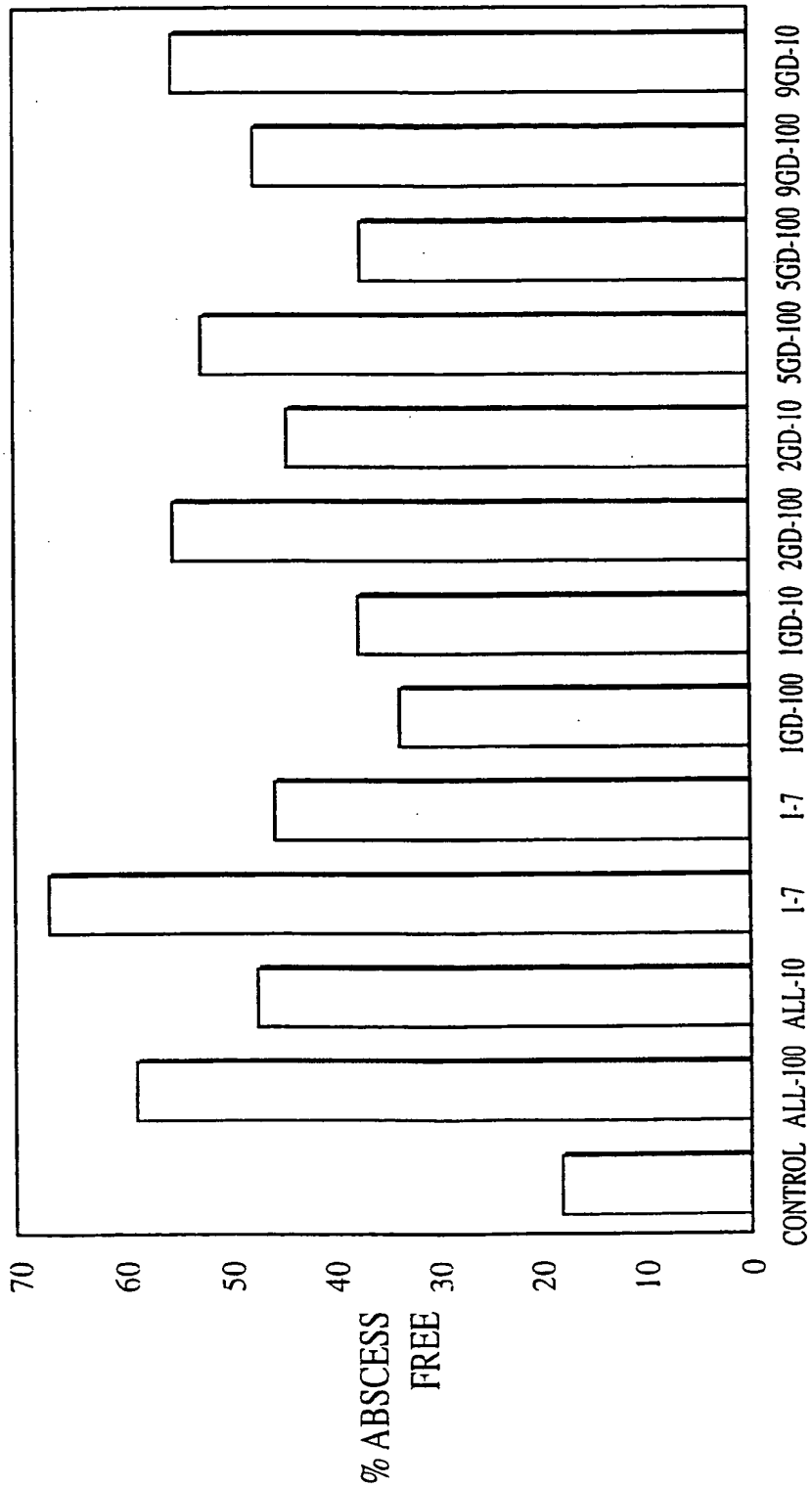
% ABSCESS FREE
70
60
50
40
30
20
10
0
CONTROL
ALL-100
ALL-10
1-7
| 100 |
1-7
1GD-100
1GD-10
2GD-100
2GD-10
5GD-100
5GD-100
9GD-100
9GD-10
10
PEPTIDE TESTED

FIG. 14

SEQUENCE LISTING

<110> Kathleen Rodgers and Gere diZerega

<120> Method for Treatment and Prevention of Infections

<130> 98,017-M2

<140> To be assigned

<141> To be assigned

<160> 41

<170> PatentIn Ver. 2.0

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<211> 8

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<210> 2

<211> 7

<212> PRT

<213> Artificial Sequence

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<210> 3

<211> 6

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Val Tyr Ile His Pro Phe

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1 5

<210> 5

<211> 6

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1 5

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1 5

<210> 7

<211> 4

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:AII(5-8)

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Ile His Pro Phe

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<210> 8

<211> 6

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<210> 9

<211> 5

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Asp Arg Val Tyr Ile

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<210> 10

<211> 4

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<220>

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Asp Arg Val

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<210> 12

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<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:AII analogue

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1 5

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<211> 3

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<213> Artificial Sequence

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<223> Description of Artificial Sequence:AII(6-8)

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His Pro Phe

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<210> 15

<211> 5

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:AII(4-8)

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Tyr Ile His Pro Phe

1 5

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<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<221> Xaa at position 1 can be Hydrogen, Arg, Lys, Ala, Or n, Ser(Acetylated), MeGly, D-Arg, or D-Lys; Xaa at positi on 2 can be Val, Ala, Leu, Nle, Ile, Gly, Pro, Aib, Acp, o

r Tyr; Xaa at position 4 can be Ile, Ala, Leu, Nle, Val, o
r Gly

<222> 1-4

<223> Description of Artificial Sequence:AII analogue

class

<400> 16

Xaa Xaa Tyr Xaa His Pro Phe

1 5

<210> 17

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1 5

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<211> 7

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1 5

<210> 19

<211> 8

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<223> Description of Artificial Sequence:AII analogue i

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1 5

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<211> 8

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<213> Artificial Sequence

<220>

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<211> 11

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<213> Artificial Sequence

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<210> 22

<211> 8

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<211> 8

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<213> Artificial Sequence

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<223> Description of Artificial Sequence:AII Analogue 5

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Asp Lys Val Tyr Ile His Pro Phe

1 5

<210> 24

<211> 8

<212> PRT

<213> Artificial Sequence

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Asp Arg Ala Tyr Ile His Pro Phe

1 5

<210> 25

<211> 8

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<213> Artificial Sequence

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<210> 26

<211> 8

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Asp Arg Val Tyr Leu His Pro Phe

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<211> 8

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<213> Artificial Sequence

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1 5

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<213> Artificial Sequence

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1 5

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<213> Artificial Sequence

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Pro Arg Val Tyr Ile His Pro Phe

1 5

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<211> 8

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1 5

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<211> 8

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<213> Artificial Sequence

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<221> PHOSPHORYLATION

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1 5

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<213> Artificial Sequence

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<221> Xaa at position 3 is Nle

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<223> Description of Artificial Sequence:AII Analogue 15

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<211> 8

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<213> Artificial Sequence

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<222> 5

<223> Description of Artificial Sequence:AII Analogue 16

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Asp Arg Val Tyr Xaa His Pro Phe

1 5

<210> 35

<211> 9

<212> PRT

<213> Artificial Sequence

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<221> homo Ser

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<400> 35

Asp Arg Val Ser Tyr Ile His Pro Phe

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<221> Xaa at position 6 is p-aminophenylalanine

<222> 6

<223> Description of Artificial

Sequence:p-aminophenylalanine 6 AII

<400> 36

Asp Arg Val Tyr Ile Xaa Pro Phe

1 5

<210> 37

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:angiotensin I

<400> 37

Asp Arg Val Tyr Ile His Pro Phe His Leu

1 5 10

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Sequence:1GD: ALa4-AII(1-7)

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<210> 39

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<212> PRT

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Sequence:2GD: Pro3 AII(1-7)

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<212> PRT

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<223> Description of Artificial

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<210> 41

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<212> PRT

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<223> Description of Artificial

Sequence: 9GD: norLeu AII(1-7)

<400> 41

Asp Arg Xaa Tyr Ile His Pro

1 5

INTERNATIONAL SEARCH REPORT

Int 'tional Application No
PCT/US 99/07654

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/08 C07K7/14 C12N5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WRAY G M ET AL: "Severe septic shock unresponsive to noradrenaline 'see comments!." LANCET, (1995 DEC 16) 346 (8990) 1604. , XP002111951 the whole document ---	1-26
X	RYDING J ET AL: "Reversal of 'refractory septic shock' by infusion of amrinone and angiotensin II in an anthracycline-treated patient." CHEST, (1995 JAN) 107 (1) 201-3. , XP002111952 the whole document ---	1-26
A	US 5 015 629 A (DIZEREGA GERE S) 14 May 1991 (1991-05-14) cited in the application -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1999	25/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 99/ 07654

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3,8-12,17-18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-3,8-12,17-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,3,4,6,7,8,19,21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,3,4,6,7,8,19,21

The scope of claims 1,3,4,6,7,8,19,21 is unduly broad and speculative. A peptide comprising at least three amino acids out of a formula consisting virtually of all variables cannot be considered to be a clear and concise definition of patentable subject-matter. (Art. 6 PCT). Furthermore, the available experimental data actually only comprise a very small part of the compounds claimed, therefore the claims are also not adequately supported by the description.
Therefore, a meaningful and economically feasible search could not encompass the complete subject-matter of the claims. Consequently, the search has been limited to angiotensin I, II and (closely) related analogues, that is those encompassed by claims 2 and 10. (Art. 17(2)(a)(ii) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte ional Application No
PCT/US 99/07654

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5015629 A	14-05-1991	NONE	

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